AMENDMENTS AND UPDATES TO HUMAN GENE TRANSFER PROTOCOLS RECOMBINANT DNA ADVISORY COMMITTEE MEETING DECEMBER 13-15, 2000

From mid-September to December, 2000	Protocols: 9709-210 9802-234 9901-280 9901-281 9905-312 9910-346 9910-352 9912-366 0002-388 0006-403 0009-412	These 11 protocols had a total number of 25 new sites/investigators added.Protocol 0006-403 had a total of ten new sites/investigators added.The remaining protocols had three or fewer new investigators/sites added per study.
	Protocols 9506-111 and 9701-209	These two protocols are closed. No individuals were enrolled under protocol 9506-111; anIND was not submitted.
	Protocols 9903-295 and 0001-377	These two protocols have been withdrawn from RAC review. Review at a RAC meeting was pending for both.
September 20, 2000 (letter date)	9906-322 Tuszynski	**A Phase I Study of NGF Ex Vivo Gene Therapy for Alzheimer's Disease** **Amendment:** Eligibility criteria have been amended to allow for enrollment of individuals with a previous history of non-nervous system cancer who are free of disease for at least two years.
September 21, 2000	9712-224	**Phase I Study of Chemokine and Cytokine Gene Modified Autologous Neuroblastoma Cells for Treatment of Relapsed/RefractoryNeuroblastoma Using an Adenoviral Vector** **Update:** Notification that study is still on hold. Received approval from the FDA and IRB to enroll one individual on compassionate ground and another as a special exception at Baylor College of Medicine.
September 22, 2000	9904-304 Hurwitz	**Pediatric Phase I Study of AdV/RSV-TK Followed by Ganciclovirfor Retinoblastoma** **Update:** Notification that an individual was enrolled in this study on a

		compassionate basis. Investigator received permission from the IRB to dose escalate the second administration of AdV/RSV-TK and to receive an additional week of ganciclovir. Informed consent was modified to reflect these changes.
October 2, 2000	9209-026 Tavel	**A Study of the Safety and Survival of the Adoptive Transfer of Genetically Marked Syngeneic Lymphocytes in HIV Infected Identical Twins.** **Update:** Study closed to new enrollment in 1994. Follow-up, life-long, is continuing. The investigator reports that: "The presence of genetically marked lymphocytes continues to fluctuate among the recipients at low to limit of quantitation levels." Peripheral blood has been negative for replication competent retrovirus (RCR). Per revised FDA requirements, samples are collected and frozen on a yearly basis for potential future RCR testing.
October 4, 2000	9706-196 Smith and Dinauer and 9908-336 Smith	**Fibronectin-Assisted, Retroviral-Mediated Transduction of CD34+ Peripheral Blood Cells with gp91 phox in Patients with X-Linked Chronic Granulomatous Disease: A Phase I Study** and **Post-Transplant Infusion of Fibronectin-Assisted, Retroviral-Mediated Gene-Marked and Ex Vivo Expanded CD34+ Placental and Umbilical Cord Blood Cells** **Update:** Received copy of response to IRB concerning potential for an allergic reaction to stem cell factor (SCF), used in the *ex vivo* expansion of cells. The investigators indicated that allergic reactions to SCF have only been observed after subcutaneous injection. In these protocols, SCF is not injected, cells are washed extensively after expansion, and biologic assays for SCF in *ex vivo* treated cells indicate that significant amounts are not present after cells are processed.
October 6, 2000	9706-196 Smith and Dinauer	**Fibronectin-Assisted, Retroviral-Mediated Transduction of CD34+ Peripheral Blood Cells with gp91 phox in Patients with X-Linked Chronic Granulomatous Disease: A Phase I Study** **Amendments:** Notification of administrative changes and clarifications in informed consent.
October 10, 2000	9910-344 Terris and 9910-345 Wilding	**A Phase I/II Dose Finding Trial of the Intraprostatic Injection of Calydon CV787, a Prostate-Specific Antigen Cytolytic Adenovirus, in Patients with Locally Recurrent Prostate Cancer Following Definitive Radiotherapy. Sponsor: Calydon, Inc.** and **A Phase I/II Dose Finding Trial of the Intravenous Injection of Calydon CV787, a Prostate-Specific Antigen Cytolytic Adenovirus, in Patients with Hormone Refractory Metastatic Prostate Cancer. Sponsor: Calydon, Inc.** **Amendments:** For both trials, study reagent will now be supplied in frozen as opposed to a lyophilized form. In addition, for protocol 9910-344 (intraprostatic injection) individuals with a PSA of up to 20 ng/ml are eligible provided that bone and CT scans are negative for metastatic disease.
October 12, 2000	9901-281 Haluska	**Phase I/II Trial of the Safety, Immunogenicity, and Efficacy of Autologous Dendritic Cells Transduced with Adenoviruses Encoding the MART-1 and gp100 Melanoma Antigens Administered With or Without Low Dose Recombinant Interleukin-2 (rIL-2) in Patients with Stage IV Melanoma. Sponsor: Genzyme Molecular Oncology** **Amendments:** In the initial clinical protocol, dendritic cells were also being pulsed, as a positive control, with a Hepatitis-B virus core peptide antigen and administered with melanoma antigen pulsed cells. This positive control will no longer be

		employed. Reasons for this change are: 1) allow for all of the dendritic cells at higher doses to be pulsed with melanoma antigens and 2) Hepatitis-B peptide is HLA-A2+ restricted and the study now allows participation of non-HLA-A2+ individuals. Due to the removal of the Hepatitis-B pulsed cells, the highest dose of modified dendritic cells has been reduced from 7.5×10^7 to 5.0×10^7. Long-term follow-up has been clarified to mean that certain tests will be performed three months post study completion; study participants will then be monitored every six months for survival until the time of death.
October 12, 2000	9906-322 Tuszynski	**A Phase I Study of NGF Ex Vivo Gene Therapy for Alzheimer's Disease** **Update:** Received copy of responses to the FDA regarding testing of producer cells for RCR, sterility, mycoplasma, and endotoxin.
October 12, 2000	9804-243 Crystal *et al.*	**Phase I Study of Direct Administration of a Replication Deficient Adenovirus vector (Ad_{GV}VEGF121.10) Containing the VEGF121 cDNA to the Ischemic Lower Limb of Individuals with Peripheral Vascular Disease. Sponsor: Parke-Davis Pharmaceutical Research** **Update:** Study has been closed at the University of Michigan trial site; PI is Dr. Sanjay Rajagopalan.
October 18, 2000	9911-356 Figlin and Belldgrun	**Phase I Bridging Trial of TG4010 as Antigen-Specific Immunotherapy in Patients with MUC-1 Positive Advanced Cancer. Sponsor: Transgene, Inc.** **Update:** Follow-up to July 28, 2000 letter regarding pox virus vector for the above trial containing a frameshift mutation resulting in the generation of MUC-1 neopeptide with an additional 169 amino acids. The frequency of this mutation in MUC-1 was discovered by an immunoplaquing assay in which individual clones were screened for the ability to produce MUC-1 that reacted with a monoclonal antibody. Only MUC-1 molecules that are correctly anchored in the cell membrane or stuck to the walls of the assay wells will react properly with the monoclonal antibody. A significant number of clones (approximately 30%) did not produce MUC-1 that reacted with the monoclonal antibody. Sequence analysis of these clones lead to the discovery of the frameshift mutation. Plasma from the 10 individuals (enrolled in Switzerland) who received lots that contained the frameshift mutation in approximately 30% of the vector genomes. An antibody response was not found to the altered MUC-1 in any individual. An antibody response to the native MUC-1 was also not found in these 10 individuals.
October 20, 2000	9701-172 Cornetta and Abonour	**High Dose Carboplatin and Etoposide Followed by Transplantation with Peripheral Blood Stem Cells Transduced with the Multiple Drug Resistance Gene in the Treatment of Germ Cell Tumors - A Pilot Study** **Update:** Received copy of response to March 6, 2000 letter from the FDA.
October 20, 2000	9202-014 Cornetta	**Retroviral-Mediated Gene Transfer of Bone Marrow Cells during Autologous Bone Marrow Transplantation for Acute Leukemia** **Update:** Received copy of response to March 6, 2000 letter from the FDA.
October 27, 2000	9412-097 Venook and Warren	**Gene Therapy of Primary and Metastatic Malignant Tumors of the Liver Using ACN53 Via Hepatic Artery Infusion: A Phase I Study. Sponsor: Schering Plough Corporation** **Update:** Study is no longer enrolling individuals at the North Shore University Hospital (PI: Dr. Harvey). Follow-up will continue on the one individual who was enrolled at this site.
October 27, 2000	9901-280	**A Phase II/III Trial of Chemotherapy Alone Versus Chemotherapy Plus SCH 58500 in Newly Diagnosed Stage III Ovarian and Primary Peritoneal Cancer**

	Buller *et al*	**Patients with ≥0.5 cm and ≤2 cm Residual Disease Following Surgery. Sponsor: Schering Corporation** **Update:** Study is no longer open at the USC Norris Comprehensive Cancer Center; PI: Dr. Garcia. No individuals were enrolled at this site.
October 27, 2000	9906-322 Tuszynski	**A Phase I Study of NGF Ex Vivo Gene Therapy for Alzheimer's Disease** **Update:** Received copy of responses to a September 20, 2000 letter from the FDA. Responses were provided to questions that dealt with, among other items, testing for RCR in both vector and vector products; assurance that adverse event reporting requirements would be followed (including to NIH OBA); and assurance that a clinical trial monitoring program is in place.
November 6, 2000	0006-403 Iskandrian *et al*	**A Randomized, Double-Blind, Placebo Controlled Study to Evaluate the Effect of Ad5FGF-4 on Myocardial Perfusion Defect Size and Safety in Patients with Stable Angina. Sponsor: Berlex Laboratories** **Amendments:** An additional primary objective for this trial: assessing the safety of a single administration of Ad5FGF-4 has been added. A safety monitoring committee (SMC) has been established for this study. This committee consists of three clinicians who will receive copies of serious adverse event reports and any follow-up reports from the sponsor. Committee may consult with any outside experts as deemed necessary. This committee will also receive summary tables of all adverse events, listings of any abnormal laboratory values, and, if requested, any additional listings (e.g., baseline medical histories). The SMC will have the ability to unblind the trial, if necessary. SMC will make recommendations to the sponsor concerning this study every six weeks regarding, for example, continuation of the study, amending the trial, or stopping. A recommendation from the SMC to halt the trial may be made at any time if "...serious adverse events and safety concerns warrant such action."
November 6, 2000	9708-207 and 9905-314 Kaufman	**Phase I Clinical Trial of a Recombinant ALVAC-CEA-B7 Vaccine in the Treatment of Advanced Colorectal Carcinoma. Sponsor: National Cancer Institute-Cancer Therapy Evaluation Program (NCI-CTEP)** and **A Phase I Trial of Intralesional RV-B7.1 Vaccine in the Treatment of Malignant Melanoma. Sponsor: NCI-Cancer Therapy Evaluation Program (NCI-CTEP)** **Update:** Received a copy of all past amendments for these two studies.
November 7, 2000	9508-118 Isner	**Accelerated Re-endothelialization and Reduced Neointimal Thickening Following Catheter Transfer of phVEGF165** **Amendments:** The following amendments have been made: 1)follow-up visits at 9, 15, and 21 months have been deleted 2)prostate exam, pelvic exam, pap smear, quality of life questionnaire and month 24 angiogram have been deleted 3)an additional eye exam has been added at 12 months post gene administration 4)chest x-ray will be performed at six instead of at three months. Schedule of two other chest x-rays has not changed 5)blood samples for determination of VEGF levels will be collected pre-gene

		administration and at week 3, and 3, 12, and 24 months post-gene administration 6)females will only be eligible if they are over 40 years of age and are not capable of child bearing **Update:** A total of 30 individuals have been enrolled in this study.Nine individuals have received a dose of1000μg, 15 individuals have received 2000μg, and six individuals have received 4000μg (out of a total of 26 proposed at this dose).
November 14, 2000	0006-402 Jensen	**Phase I Study to Evaluate the Safety of Cellular Immunotherapy for Recurrent/Refractory Neuroblastoma Using Genetically-Modified Autologous CD8+ T Cell Clones** **Amendments:** Changes were made to the clinical protocol in response to the FDA. These changes include: 1) changes to the inclusion/exclusion criteria for histologic verification of neuroblastoma at original diagnosis; 2) negative pregnancy test and use of effective contraception; 3) history of ganciclovir allergy or intolerance; and 4) disseminated neuroblastoma that is refractory to 1st line therapy is further clarified. Stopping rules have been amended to 1) include any grade IV toxicity that does not resolve to grade II or less with ganciclovir/steroid administration; 2) if adequate cells are not obtained from the first three individuals enrolled within 100 days of leukapheresis; and 3) if the incidence of grade IV or higher toxicity exceeds 33% in the individuals enrolled (reduced from 50%). Maximum time allowed to recover from salvage therapy, and to remain eligible for enrollment in this study, has been defined as 100 days. Plasmid vector has been modified to express the two encoded genes from separate promoters. A CMV promoter is used for the hygromycin resistance-thymidine kinase genetic fusion and the human elongation factor 1α promoter is now used for the CE7R chimeric immunoreceptor. This change was made due to a lack of the original plasmid demonstrating sufficient expression of the chimeric immunoreceptor (less than 10% co-expression in hygromycin resistant cells). This re-designed plasmid demonstrates greater than 50% co-expression in hygromycin resistant cells.
November 17, 2000	9707-204 Hickstein and Bauer	**Retrovirus-Mediated Transfer of the cDNA for Human CD18 into Peripheral Blood Repopulating Cells of Patients with Leukocyte Adherence Deficiency** **Update:** Notification that study is now closed to new enrollment.Two individuals were enrolled in this study. Both individuals are received gene modified cells over one year ago. Neither individual demonstrated the presence of CD18 positive cells past two months of the single infusion.

Responses received regarding recommendations from September 2000 RAC meeting & notifications of initiation

October 19 and 23, 2000	0006-404 Moss	**A Multicenter, Double-Blind, Placebo-Controlled, Phase II Study of Aerosolized AAVCF in Cystic Fibrosis Patients with Mild Lung Disease. Sponsor: Targeted Genetics** Received a response from Targeted Genetics to the observations and recommendations made at the September 2000 RAC meeting. Also received amendments to the clinical protocol in response to changes requested by the FDA. A 150 day follow-up visit has been added for evaluation of safety. Additional sputum samples will be collected to assess viral shedding. Changes were also made to the clinical protocol to incorporate information communicated at the September RAC meeting.36 individuals will now be enrolled in this study: 18 will receive the AAVCF construct and 18 a placebo.

		(See RAC meeting material for additional information.)
October 26, 2000	0007-407 Rosengart	**A Phase I, Double-blind, Placebo Controlled, Escalating Dose, Multi-center Study of Ad2/Hypoxia Inducible Factor (HIF)-1a/VP16 Gene Transfer Administration by Intramyocardial Injection During Coronary Artery Bypass Grafting (CABG) Surgery in Patients with Areas of Viable and Underperfused Myocardium not Amenable to Bypass Grafting or Percutaneous Intervention. Sponsor: Genzyme Corporation** Received a response from Genzyme Corporation in response to the observations and recommendations made at the September 2000 RAC meeting. (See RAC meeting material for additional information.)
November 6, 2000	0003-390 Kohn	**Retroviral-Mediated Transfer of the RevM10 and FX Genes into CD 34+ Cells from the Bone Marrow of HIV-1 Infected Children** Notification that investigator is initiating study. Copies of updated clinical protocol and informed consent were received.
November 7, 2000	0002-378 McQuone	**A Multicenter, Open-Label, Multiple Administration, Study of the Safety, Tolerability and Efficacy of IFNa/IL-12 Combination Gene Therapy in Patients with Squamous Cell Carcinoma of the Head and Neck (SCCHN). Sponsor: Valentis, Inc.** Notification that the first individual was enrolled on October 3, 2000.